UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,084	04/07/2006	Mary Collins	M0274.70042US02	7531

23628 7590 11/26/2007

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
11/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,084	COLLINS ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-51* is/are pending in the application.

4a) Of the above claim(s) *45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-44 and 46-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed on 09/13/2007, are acknowledged.

Claims 35 – 51 are pending.

Applicant's election without traverse of Group I, claims 35 – 44 and 46 – 51, in the reply filed on 09/13/2007 is acknowledged.

Applicant further elects the species of PD1-35 as the antibody and human PD-1 (SEQ ID NO:41) as the species of PD-1.

Claim 45 is withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 35 – 44 and 46 – 51are presently under consideration.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

3. The following is a quotation of the **second paragraph of 35 U.S.C. 112**.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 35 – 44 and 46 – 51 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 35 – 44 and 46 – 51 are indefinite in the recitation of "modulating" because it is ambiguous as to the direction (positive or negative) or degree of said modulating.

B. Claim 39 is indefinite in the recitation of "PD-L." It appears that the term is intended to denote a ligand of PD-1; however, it is unclear whether the term is limited to PD-L1, PD-L2, or both, or if it is intended to encompass other possible PD-1 ligands yet to be discovered. "PD-L" is not an art-recognized term, and the specification does not provide a definition, therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. For examination purposes, it is assumed that PD-L encompasses at least PD-L1.

Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

5. The following is a quotation of the **first paragraph of 35 U.S.C. §112**:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 43 is rejected under **35 U.S.C. §112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

It is apparent that antibodies PD1-17, PD1-28, PD1-33, PD-1-35, and PD1-F2 are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty would satisfy the deposit requirement made herein.

In addition to the conditions under the Budapest Treaty, applicant is required to provide assurance that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

7. Claims 35 – 42, 44, and 46 – 51 are rejected under **35 U.S.C. §112, first paragraph**, because the specification, while being enabling for the claimed method utilizing an antibody comprising all six CDRs (or both heavy and light chain variable regions) of one of antibodies PD1-17, PD1-28, PD1-33, PD-1-35, and PD1-F2, wherein the antibody specifically binds to PD-1 of amino acid sequence SEQ ID NO: 41 or 56,

does not reasonably provide enablement for:

A. an antibody defined by a sequence of a single complementarity-determining region (CDR) or a single variable region; or

B. an antibody which specifically binds to an amino acid sequence that is at least 95% identical to any sequence of at least 100 of contiguous amino acids of SEQ ID NO: 41 or 56.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation. An ability of the claimed antibody to bind to a specific antigen is considered to be an essential feature of the claimed invention; however, undue experimentation would be required to make and use the claimed antibodies, because the binding specificity of the antibodies as encompassed by the generic language of the instant claims is highly unpredictable.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

A. The instant claims are directed to an antibody defined by a sequence of a single complementarity determining region (CDR), or a single CDR and a single variable region.

An ability of the claimed antibody to bind to a specific antigen is considered to be an essential feature of the claimed invention. However, it is well established in the art that the formation of an intact antigen-binding site generally requires all six CDRs. Specific interaction with the antigen requires the association of the complete heavy and light chain variable regions of the antibody, each of which consists of three CDRs, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce an antibody having antigen-binding function, and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function, as evidenced by numerous references (e.g. Rudikoff et al. 1982, Proc. Natl. Acad. Sci. USA, , 79: 1979 – 1983; see entire document, in particular, e.g. the Abstract; Adair et al., 2003, US Patent No. 6,632,927; see entire document, in particular, e.g. columns 2 – 3, bridging paragraph; and Panka et al., 1988, Proc. Natl. Acad. Sci. USA, 85: 3080 – 3084; see entire document, in particular, e.g. the Abstract), which all teach that alteration of a single amino acid in an antibody results in the loss or a major change of the antigen-binding function.

Therefore, it is unpredictable whether antibodies as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions, have the antigen-binding function. The specification provides

insufficient direction or guidance regarding how to produce functional antibodies broadly defined by the claims. Undue experimentation would be required to make and use the invention commensurate with the scope of the claims from the written disclosure alone.

B. The specification disclosure is insufficient to enable one skilled in the art to practice the invention without an undue amount of experimentation, because it is unpredictable whether an antibody that binds to a polypeptide of the recited amino acid sequence will bind to a variant that is at least 95% identical to any sequence of at least 100 of contiguous amino acids of the recited sequence. For example, Lederman et al. (Molecular Immunology, 1991, 28: 1171 – 1181; see entire document, in particular, e.g. the Abstract) and Colman P.M. (Research in Immunology, 1994, 145: 33 – 36; see entire document, in particular, e.g. page 34) teach that a single amino acid substitution in a polypeptide ablates binding of an antibody. The instant specification fails to provide sufficient guidance regarding how to make and use antibodies which specifically bind to an amino acid sequence that is distinct from human of mouse PD-1, including antibodies which specifically bind to an amino acid sequence that is at least 95% identical to any sequence of at least 100 of contiguous amino acids of SEQ ID NO: 41 or 56.

Because of this lack of guidance, extensive experimentation by those skilled in the art would be required to determine which sequence modifications of SEQ ID NOS: 41 or 56 retain binding by antibodies within the scope of the instant claims. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

To conclude, reasonable correlation must exist between the scope of the claims and scope of enablement set forth. See In re Fisher, 166 USPQ 18 24 (CCPA 1970). Without sufficient guidance, the complete structure of the claimed antibodies is

unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

8. Claims 35 and 37 are rejected under **35 U.S.C. §112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following ***Written Description*** rejection is set forth herein.

Applicant is not in possession of an antibody which specifically binds to an amino acid sequence that is at least 95% identical to any sequence of at least 100 of contiguous amino acids of SEQ ID NO: 41 or 56.

The instant claims do not provide sufficient structural and functional characteristics of the genus of antibodies encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure. Consequently, the specification does not describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the

genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant is not in possession of the claimed method, because Applicant is not in possession of a polypeptide of an amino acid sequence that is at least 95% identical to any sequence of at least 100 of contiguous amino acids of SEQ ID NO: 41 or 56. Applicant has disclosed two PD-1 polypeptides, and thus has disclosed only two "variants". In the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Attwood (Science, 2000, 290: 471 – 473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech., 2000, 18: 34 – 39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Thus the recitation of percent identity language does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of **35 U.S.C. §102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 35 – 44 and 46 – 51 are rejected under **35 U.S.C. §102(e)** as being anticipated by Wood et al. (US Patent 6,808,710; filed 08/23/2000; priority date 08/23/1999; see entire document), as evidenced by the instant specification at pages 13 – 14.

Wood et al. teach and claim a method for downmodulating an immune response comprising contacting an immune cell with an antibody to PD-1, wherein the antibody is crosslinked or immobilized (e.g. claims 1 – 9). In particular, Wood et al. teach anti-PD-1

antibody PD1-17 (e.g. Example 17 at column 86; more specifically, lines 49 – 61), i.e. the same antibody as recited in the instant claims 10 and 16.

Since antibody PD1-17 taught by Wood et al. is the same as the instantly recited antibody PD1-17, it inherently possesses the same structure (i.e. the same amino acid sequences), as well as functional properties, such as specificity, affinity constant, and ability to block binding between PD-1 and PD-L1. Furthermore, the instant specification provides evidence that antibody PD1-17 comprises amino acid sequences SEQ ID NOS: 2, 4, and 19 (Tables 1 – 3 at pages 13 – 14). In addition, Wood et al. specifically teach that the PD1-17 antibody inhibits the binding of B7-4 (an art-recognized alternate name of PD-L1) to PD-1 with an IC_{50} of between 10^{-8} M and 10^{-9} M (column 86, lines 59 – 61), i.e. less than 10 nM. The PD1-17 antibody taught by Wood et al. is of the $IgG_{1\kappa}$ subclass, as evidenced e.g. by the instant specification at page 14 (last complete sentence on the page).

Wood et al. further teach immobilization of antibodies and proteins on microtiter plates (which are usually made of polystyrene, as one of skill in the art is aware) or dextran chips (e.g. column 61 lines 12 – 32 and column 82, lines 36 – 54). Wood et al. also teach that anti-PD-1 antibodies may be used together with anti-CD3 antibodies on beads (e.g. column 50 lines 25 – 38).

Wood et al. further teach that both human and mouse PD-1 are within the scope of their invention (e.g. column 19 lines 40 – 43); therefore, antibodies that specifically bind to both human and mouse PD-1 (SEQ ID NOS: 41 and 56) are inherent in the teachings of Wood et al.

In view of the above, the reference teachings anticipate the instant claimed invention.

11. The nonstatutory **double patenting** rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the."right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 35 – 44 and 46 – 51 are rejected on the ground of nonstatutory obviousness-type **double patenting** as being unpatentable over claims 1 – 9 of U.S. Patent No. 6,808,710 and claims 1 – 7 of US Patent No. 7,029,674. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are directed to the same or nearly the same methods of modulating an immune response by administering anti-PD-1 antibodies.

13. Claims 35 – 44 and 46 – 51 are provisionally rejected on the ground of nonstatutory obviousness-type **double patenting** as being unpatentable over claims 1 – 19 of copending Application USSN 11/357,434 and claims 1 – 26 of copending Application USSN 11/514,328. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are directed to the same or nearly the same methods of modulating an immune response by administering anti-PD-1 antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 35 – 44 and 46 – 51 are directed to an invention not patentably distinct from the claims of commonly assigned U.S. Patents No. 6,808,710 and 7,029,674, and Applications USSN 11/357,434 and 11/514,328, for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned Patents and Applications, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

15. Conclusion: no claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ilia Ouspenski

ILIA OUSPENSKI, Ph.D.
Patent Examiner
Art Unit 1644

November 20, 2007